IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:	)	Before the Examiner
Stefano Carlino	)	Elli Peselev
	)	
Serial No. 10/523,657	)	Group Art Unit: 1623
	)	
Filing Date: February 4, 2005	)	Attorney Docket: LABM-10
	)	
PROCESS FOR PREPARING A STERILE HIGH MOLECULAR WEIGHT HYALURONIC ACID FORMULATION	)	November 6, 2009

APPEAL BRIEF 37 C.F.R. §41.37 & MPEP 1207.04

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Sir:

This Appeal Brief is hereby filed pursuant to the provisions of MPEP 1207.04. Applicant's Appeal Brief fully complies with new rule 36 C.F.R. §41.37. No additional extensions of time are believed to be necessary, but if any are deemed to be due, please charge the fees therefore to Deposit Account 12-2424.

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November 6, 2009
Date

I. REAL PARTY IN INTEREST
(37 C.F.R. §41.37(e)(1))

The real party in interest in this appeal is the Assignee, Laboratoire Medidom S.A.

II. RELATED CASES
(34 C.F.R. §41.37(e)(2))

With respect to other cases that are related to, or will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal; there are none.

III. JURISDICTIONAL STATEMENT
(34 C.F.R. §41.37(e)(3))

The statute under which this appeal is taken is 35 U.S.C. §134(a) (Appeal to the Board of Patent Appeals and Interferences).

The Office Action setting out the rejection on appeal was issued on July 6, 2009.

The Notice of Appeal, together with a petition for extension of time of one (1) month under 37 C.F.R. §1.136(a) (PTO/SB/22), is being filed herewith.

The Appeal Brief is being filed on November 6, 2009.

IV. TABLE OF CONTENTS
(37 C.F.R. §41.37(e)(4))

V. TABLE OF AUTHORITIES
(37 C.F.R. §41.37(e)(5))

There are none cited.

VI. STATUS OF AMENDMENTS
(37 C.F.R. §41.37(e)(7))

No amendments were filed after the final rejection.

VII. GROUNDS OF REJECTION TO BE REVIEWED
(37 C.F.R. §41.37(e)(8))

Claims 1 and 4-9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,489,467 in view of U.S. Patent No. 5,503,848.

Claims 1 and 4-9 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,489,467 in view of U.S. Patent No. 5,503,848.

VIII. STATEMENT OF FACTS
(37 C.F.R. §41.37(e)(9))

The present invention is directed to a process for preparing a sterile ready-to-use aqueous pharmaceutical formulation comprising a high molecular weight hyaluronic acid salt at a specified concentration [p 2 [0026]], comprising the steps of providing an aqueous formulation comprising high molecular weight hyaluronic acid salt at a concentration of less than the specified concentration[p 2 [0027]; Figure 1, step 4]; passing the aqueous formulation through a filter having a pore size of less than 0.45 μm [p 2 [0028]; p 3 [0050]] and greater than 0.1 μm [p 3 [0050]; Figure 1,

step 7]; concentrating the aqueous formulation by applying a vacuum and boiling off water until said specified concentration is reached [p 2 [0029]]; wherein from the concentration step the pharmaceutical formulation is filled directly into sterile recipients ready for pharmaceutical use [p 2 [0030]], or into sterile tanks and subsequently directly into sterile recipients ready for pharmaceutical use [p 4 [0058]; Figure 1, steps 14-16; original claim 4].

Previously used methods for the preparation of ready-to-use pharmaceutical formulations of hyaluronic acid involve measuring out a defined precise quantity by weight of hyaluronic acid, which is then mixed with a precise volume of water and precise quantities of excipients [p 1 [0016]]. The formulation is then filled into syringes and vials, and subsequently sterilized by autoclave, with the associated problems of degradation of hyaluronic acid molecular chains on heat sterilization [p 1 [0016]]. Even where the preparation of the ready-to-use aqueous formulation of hyaluronic acid salt is carried out starting from a pre-sterilized powder of hyaluronic acid salt [p 1 [0020]], this powder must be measured in an accurate amount and added to a precise quantity of water, and precise amounts of excipients [p 1 [0016]], in order to get the required accurate concentration of the pharmaceutical formulation necessary for medical applications [p 2 [0033]]. The measuring and mixing of the sterilized powder necessarily requires removal of the sterilized powder from the storage vessel transfer to a measuring vessel, and to the vessel in which it will be

mixed with water. Not only is this process cumbersome, but also in all of the steps there is introduced a risk of contamination of the sterile powder [p 1 [0031]].

An alternative process for preparing ready-to-use hyaluronic acid pharmaceutical formulations is reported in US 5,093,487 (cited in the present application) [p 2 [0023]], which involves filtering a concentrated solution of hyaluronic acid aqueous formulation by means of multiple passes through a 0.2 μm filter, so as to irreversibly reduce the viscosity of the hyaluronic acid [p 2 [0023]]. The process of US 5,093,487 not only causes an irreversible reduction of the viscosity, but also it is not possible to control the homogeneous viscosity of the hyaluronic acid salt solution after such multiple filtration steps, such that viscosity variations may occur from one batch of hyaluronic acid formulation to another [p 2 [0022] [0023]]. This irreversible reduction of the viscosity of the hyaluronic acid, and the variability of viscosity of batches of sterilized formulation, are undesirable for pharmaceutical applications of hyaluronic acid such as intra-articular and ocular applications [p 2 [0023]].

Whereas, in contrast to the previously taught methods for preparing ready-to-use pharmaceutical formulations of hyaluronic acid, the process of the present invention as claimed allows for the preparation of sterile pharmaceutical formulations of high molecular weight hyaluronic acid salt directly ready for pharmaceutical use, in which the required properties of high molecular weight of

hyaluronic acid and determined high viscosity are maintained [p 2 [0030], [0032], [0033]].

No additional preparation or sterilisation steps are required before pharmaceutical use of the hyaluronic acid salt formulations prepared to the present invention [p 1 [0017], [0022]; p 2 [0030], [0035]]. The process of the present invention avoids the need for additional manipulations of weighing out accurately specific amounts of sterilized concentrated sodium hyaluronic powder [p 1 [0016]], mixing the powder with a defined precise volume of water and precise quantities of excipients, since the concentration of the formulation is accurately monitored to arrive at the desired specified concentration during the vacuum concentration step [p 2 [0033]]; and avoids the associated risks of contamination due to the removal of the sterilized hyaluronic acid salt powder from a storage vessel, transfer to a measuring vessel and then transfer to a vessel in which the powder would be mixed with water, before finally being filled into recipients for pharmaceutical use, encountered in the preparation of pharmaceutical formulations by the conventional methods [p 1 [0016], [0017], [0020], [0022], [0023]]. In order to meet health authority standards for administration in the human body, the aqueous formulations prepared from sterilized hyaluronic acid salt powder by prior art conventional methods must be subjected to further sterilization, such as by autoclaving of the formulation filled in vials or syringes before it may be used for pharmaceutical use [p 1 [0016]]. This is

not necessary for the sterile ready for pharmaceutical use formulations of high molecular weight hyaluronic acid salt of the present invention [p 2 [0030]].

IX. ARGUMENT
(37 C.F.R. §41.37(e)(10))

(1) With respect to the Examiner's rejection of the pending claims, 1 and 4 to 9 on grounds of non-statutory obviousness-type double patenting over claims 1 to 23 of US 6,489,467 in view of US 5,503,848, the Applicant cannot agree with the examiner's interpretation of the cited documents, and the rejection is respectfully traversed.

At the outset it must be highlighted that the present invention as claimed is not simply the use of evaporation under vacuum to concentrate a solution comprising hyaluronic acid [p 7, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007], but, on the contrary, lies in the provision of a process for preparing sterile ready-to-use aqueous pharmaceutical formulations comprising a high molecular weight hyaluronic acid salt (HA) at a specified concentration [p 4, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007], involving the specific combination of the steps of; providing an aqueous formulation comprising high molecular weight HA at a concentration of less than the desired specified concentration; passing said aqueous formulation through a filter having a pole size of less that 0.45 μm and greater than 0.1 μm; concentrating said aqueous formulation by applying a vacuum and boiling of water until said specified concentration is reached [p 4, Applicant's reply mailed on

December 6, 2007 to Office Action mailed September 7, 2007]; and after the concentration step, filling the pharmaceutical formulation directly into sterile recipients ready for pharmaceutical use, or into sterile tanks and subsequently directly into sterile recipients ready for pharmaceutical use [p 5, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 4 and 7-8, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007].

Contrary to the presently claimed invention, US 6,489,467 claims a process for purifying HA from a biological source, which process involves steps of diafiltration (step a) and the removing of cells (step b) from an aqueous solution of hyaluronic acid obtained from a biological source, followed by subsequently sterilizing the thus purified HA containing solution (step c) [p 2, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. In the method claimed by US 6,489,467 the sterilisation step may be carried out by passing the purified HA containing solution through a 0.2 μm filter (claim 27 of US 6,489,467) [p 2, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. According to US 6,489,467 the thus obtained solution is freeze dried to obtain a dry powder of purified HA (e.g., as claimed in claim 9 of US 6,489,467) [p 2, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. US 6,489,467 does not claim, nor does it make obvious in any way, the

process for preparing a sterile ready-to-use aqueous pharmaceutical formulation of HA at a specified concentration according to the present invention involving the specific combination of steps of providing an aqueous formulation comprising high molecular weight HA at a concentration of less than the specified concentration; passing the aqueous formulation through a filter having a pore size of less than 0,45 μm and greater than 0.1 μm; concentrating said aqueous formulation by applying a vacuum and boiling of water until said specified concentration is reached; and wherein after the concentration step, the pharmaceutical formulation is filled directly into sterile recipients ready for pharmaceutical use[p 4, 6 and 7-8, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007; p 3, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

It must further be highlighted that US 6,489,467 teaches a method of preparing purified hyaluronic acid, in the form of a dry powder, which freeze-dried powder may subsequently be used for the preparation of pharmaceutical preparations in a conventional manner (see e.g. example col. 8 lines 3 to 5 and col. 9 lines 16 to 18 US 6,489,467) [p 3, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. In other words, before the concentrated HA powder of the process of US 6,489,467 can be used for pharmaceutical applications it must be prepared further into a ready-to-use pharmaceutical formulation of pharmaceutical concentration in the conventional manner [p 3, Applicant's reply mailed on June 9,

2008 to Office Action mailed January 9, 2008]. The ordinarily skilled person reading US 6,489,467 has, accordingly, a method for purifying high molecular weight hyaluronic acid from a biological source, and for preparing pharmaceutical formulations of this purified HA by conventional methods starting from the freeze-dried purified HA powder, and the ordinarily skilled person has no reason whatsoever to look for any other method for preparing pharmaceutical formulations of HA [p 3, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

Since the skilled person is taught by US 6,489,467 to prepare pharmaceutical formulation from the freeze-dried powder of HA, it is totally unobvious for the skilled person to decide to stop following the method of US 6,489,467 after the step of sterilisation by filtration, and then instead of following the teaching of US 6,489,467, to subject this sterilized solution to a step of concentration under vacuum to a specific accurate pharmaceutical concentration, followed by filling it directly into sterile recipients with the aim to provide an aqueous pharmaceutical formulation of high molecular weight HA ready for pharmaceutical use, as required by the present invention, as claimed [p 3-4, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

The Examiner cites in combination US 5,503,848 which is directed to a spongy material consisting essentially of lyophilised hyaluronic acid or its

derivatives, taught by US 5,503,848 to be useful in microsurgical practice, particularly as an implant for use in the repair of tympanic perforations. A process for preparing the disks of spongy hyaluronic acid material is described at col. 10 of US 5,503,848. Contrary to the Examiner's assertions, US 5,503,848 does not describe any step of concentrating a solution of hyaluronic acid by a vacuum concentration process; let alone any process whereby a filter-sterilized solution of HA, sterilized by filtration through a filter having pore size less than 0.45 μm and greater than 0.1 μm, is concentrated by applying a vacuum and boiling off water until the specified concentration is reached, as required by the claims of the present application.

Indeed, the first step of the preparation process of US 5,503,848, referred to by the Examiner, is a step of "Dissolution of the active principle," whereby, "hyaluronic acid, or one of its estereal derivatives, is dissolved in water for injectable preparations, so as to reach a concentration ranging between 1 mg/ml and 40 mg/ml" (US 5,503,848 col.10, lines 25-27). In other words, in US 5,503,848, the hyaluronic acid solution of the desired concentration range (between 1mg/ml and 40 mg/ml) is arrived at simply by dissolving HA or one of its derivatives, in water up to the desired concentration. There is no description, suggestion, whatsoever of any step of concentrating a HA solution to a desired concentration by vacuum concentration methods.

In the process of US 5,503,848 the reason that the apparatus is equipped also with a "vacuum/nitrogen-pressure/ sterile filtrate system" is so that in the next step, "2. Solution filtration", the solution containing HA can be filtered through a sterilising membrane having a porosity of 0.2 μm. (US 5,503,848, col.10, lines 28-32). It must be remembered that in order to achieve filtration of aqueous solutions of hyaluronic acid through such microporous sterilising membranes (e.g. porosity 0.2 μm) it is necessary to carry out the filtration with a vacuum/nitrogen-pressure filtration system, otherwise the aqueous HA solution will not pass through the microporous membrane. Accordingly, it is necessary for the apparatus of US 5,503,848 to have a vacuum/nitrogen-pressure/sterile filtration system in order to carry out the filtration step.

Accordingly, US 5,503,848 does not disclose any step for concentration of a filter-sterilized solution of HA, by applying a vacuum and boiling off water until a specified concentration is reached, as required by the claims of the present invention.

Further, US 5,503,848 does not provide any teaching whatsoever for a step of filling a pharmaceutical formulation of HA directly after a concentration step into sterile recipients for pharmaceutical use.

Therefore, not only would the person of ordinary skill in the are on reading US 6,489,467 have no reason to look for any alternative method for preparing sterile aqueous formulations of high molecular weight HA; but also the person of ordinary

skill in the art if then confronted with the teaching of US 5,503,848 would be completely unable to arrive at the process of the present invention.

Accordingly, the Examiner's rejection of claims 1 and 4 to 9 on grounds of non-statutory obviousness-type double patenting is respectfully traversed.

(2) With respect to the Examiner's rejection of the pending claims 1 and 4 to 9 on grounds of obviousness under 35 USC 103(a) over US 6,489,467 in view of US 5,503,848, the Applicant cannot agree with the Examiner's interpretation of the cited prior art documents, and the rejection is respectfully traversed:

US 6, 849,467 is directed to a process for obtaining a purified high molecular weight hyaluronic acid powder, involving steps of diafiltration and removing of salts from an aqueous solution of hyaluronic acid obtained from a biological source, followed by sterilising the obtained HA containing solution by passing through a 0.2 μm filter [p 5, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007; p 4, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. US 6,849,467 teaches that the filter sterilized HA containing aqueous solution may be freeze-dried to obtain a dry powder of HA in purified form (see for example page 10 last 5 lines of US 6,849,467) [p 5, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007; p 4, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. The process taught by US 6,849,467 produces a sterilized purified

dry powder of HA [p 4, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007], which it is taught may subsequently be used for preparing pharmaceutical compositions [p 6, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 5, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007].

US 6,849,467 does not teach or even suggest in any way a step of concentrating a filter-sterilized aqueous solution of HA to specific accurate pharmaceutical concentration, by applying a vacuum and boiling off water until the specified concentration is reached [p 6, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 6, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007]; nor is it taught or even suggested to take any step toward filling such a sterilized pharmaceutical formulation of HA, at a specific accurate pharmaceutical concentration, directly into sterile recipients ready for pharmaceutical use [p 5, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 6, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

It is also highlighted that since US 6,849,467 teaches a method of preparing purified hyaluronic in the form of a dry powder, which can then be used for the preparation of pharmaceutical composition in a conventional manner [p 6, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p

5, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007], i.e., by weighing out an accurate quantity of the dry HA powder and dissolving this in an accurate volume of water, with the addition of accurately measured quantities of desired excipients to provide an aqueous pharmaceutical formulation [p 6, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 5-6, Applicant's reply mailed on December 6, 2007 to Office Action mailed September 7, 2007], the skilled person reading US 6,849,467 is thus specifically taught how to go about preparing a pharmaceutical formulation of HA, and none of the cited documents provide the skilled person with any reason to look for an alternative method for preparing sterile aqueous formulations of high molecular weight HA ready for pharmaceutical use [p 5-6, Applicant's reply mailed on June 5, 2007 to Office Action mailed March 6, 2007; p 5-6, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]. Since the skilled person is taught by US 6,849,467 how to prepare pharmaceutical formulations from the freeze-dried powder of HA, it would be totally unobvious for the skilled person to instead stop at the step of sterilisation by filtration of step (c) and, instead of following the teaching of US 6,849,467, to the contrary to concentrate an aqueous of step (c) solution by applying a vacuum and boiling off water until a pre-specified accurate pharmaceutical concentration is reached [p 6, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008]; and then filling the

formulation directly into sterile recipients, as required by the present invention, as claimed, [p 6, Applicant's reply mailed on June 9, 2008 to Office Action mailed January 9, 2008].

Moreover, none of the steps of the present invention, as claimed, of (i) concentrating a filter-sterilized aqueous formulation of high molecular weight HA, having a concentration of less than the desired specified pharmaceutical concentration, by concentration under vacuum to a specific accurate pharmaceutical concentration, followed by (ii) filling directly into sterile recipients ready-for pharmaceutical use, are disclosed or even suggested in any of the cited documents.

The Examiner cites US 5,503,848, in combination, which is directed to a spongy material consisting essentially of lyophilised hyaluronic acid or its derivatives, taught by US 5,503,848 to be useful in microsurgical practice, particularly as an implant for use in the repair of tympanic perforations. A process for preparing the disks of spongy hyaluronic acid material is described at col. 10, lines 21 to 59, of US 5,503,848. Contrary to the Examiner's assertions, US 5,503,848 does not describe any step of concentrating a solution of hyaluronic acid by a vacuum concentration process; let alone any process whereby a filter-sterilized solution of HA, sterilized by filtration through a filter having pore size less than 0.45 μm and greater than 0.1 μm, is concentrated by applying a vacuum and boiling off

water until the specified concentration is reached, as required by the claims of the present application.

Indeed, the first step of the preparation process of US 5,503,848 referred to by the Examiner, is a step of "Dissolution of the active principle," whereby, "hyaluronic acid, or one of its estereal derivatives, is dissolved in water for injectable preparations, so as to reach a concentration ranging between 1 mg/ml and 40 mg/ml" (US 5,503,848 col.10, lines 25-27). In other words, in US 5,503,848, the hyaluronic acid solution of the desired concentration range (between 1mg/ml and 40 mg/ml) is arrived at simply by dissolving HA or one of its derivatives, in water up to the desired concentration. There is no description, suggestion, whatsoever of any step of concentrating a HA solution to a desired concentration by vacuum concentration methods.

In the process of US 5,503,848 the reason that the apparatus is equipped also with a "vacuum/nitrogen-pressure/ sterile filtrate system" is so that in the next step, "2. Solution filtration," the solution containing HA can be filtered through a sterilizing membrane having a porosity of 0.2 μm. (US 5,503,848, col.10, lines 28-32). It must be remembered that in order to achieve filtration of aqueous solutions of hyaluronic acid through such microporous sterilising membranes (e.g., porosity 0.2 μm) it is necessary to carry out the filtration under vacuum/nitrogen-pressure otherwise the aqueous HA solution will not pass through the microporous

membrane. Accordingly, it is necessary for the apparatus to have a vacuum/nitrogen-pressure/sterile filtration system in order to carry out this filtration step.

It is further highlighted that in the process of US 5,503,848 a sterilized solution of HA, or derivatives thereof, is prepared by the dissolution of HA in water for injection up to a concentration in the range of 1 mg/ml to 40mg/ml in a first step; and then this solution, is then sterilized by filtration through a membrane of a porosity of 0.2 μm in a subsequent, second step. US 5,503,848 is silent with respect to the molecular weight of the hyaluronic acid used. However, it should be noted that if US 5,503,848 were to use high molecular weight hyaluronic acid, as required for the sterile pharmaceutical formulations of the present invention, then at the concentrations of high molecular weight HA required for providing the high viscosity aqueous HA formulations for pharmaceutical use (e.g., 1 to 3 % wt/w HA) not all of the HA would pass through a filter of 0.2 μm pore size as taught in the sterilisation step of US 5,503,848. This would result in significant reduction of the concentration of HA and irreversible degradation of the high molecular weight HA, i.e., reduction of molecular weight of the HA and reduction of viscosity, which is not acceptable for pharmaceutical applications of aqueous high molecular weight hyaluronic acid formulations such as intra-articular and ocular applications.

Accordingly, US 5,503,848 does not disclose any step for concentration of a filter-sterilized solution of HA, by applying a vacuum and boiling off water until a specified concentration is reached, as required by the claims of the present invention.

Further, US 5,503,848 does not provide any teaching whatsoever for a step of filling a pharmaceutical formulation of HA directly after a concentration step into sterile recipients for pharmaceutical use.

Therefore, not only would the person of ordinary skill in the art on reading US 6,489,467 have no reason to look for any alternative method for preparing sterile aqueous formulations of high molecular weight HA; but the person of ordinary skill in the art, if then confronted with the teaching of US 5,503,848, would be completely unable to arrive at the process of the present invention by combining the teachings thereof.

Accordingly, the Examiner's rejection of claim 1 and 4 to 9 on grounds of obviousness under 35 USC 103(a) over US 6,489,467 in view of US 5,503,848 is respectfully traversed.

Respectfully submitted,

Date: November 6, 2009

By: _____

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KD_IM-1933187_1.DOC

APPENDIX

CLAIM SECTION

(37 C.F.R. §41.37(e)(11))

1. (Rejected) A process for preparing a sterile ready-to-use aqueous pharmaceutical formulation comprising a high molecular weight hyaluronic acid salt (HA) at a specified concentration, comprising the steps of:

- providing an aqueous formulation comprising high molecular weight HA at a concentration of less than the specified concentration;

- passing said aqueous formulation through a filter having a pore size less than 0.45 μm; and greater than 0.1 μm;

- concentrating said aqueous formulation by applying a vacuum and boiling off water until said specified concentration is reached; and

- after the concentration step, filling the pharmaceutical formulation directly into sterile recipients ready for pharmaceutical use, or into sterile tanks and subsequently directly into sterile recipients ready for pharmaceutical use.

2. (Cancelled)

3. (Cancelled)

4. (Rejected) Process according to claim 1, wherein the vacuum is at a pressure in the range of 30 to 60 millibars.

5. (Rejected) Process according to claim 1, wherein the average molecular weight of HA is in the range of 800'000 to 5'000'000 Daltons.

6. (Rejected) Process according to claim 1, wherein the filter has a pore size in the range of 0.22 μm to 0.1 μm.

7. (Rejected) Process according to claim 1, wherein, during the concentration step, the concentration of HA is measured in real time and the vacuum boiling process is stopped automatically when the specified concentration is measured.

8. (Rejected) Process according to claim 1, wherein the HA concentration is measured with a spectrophotometer sensing wave radiation absorption in the formulation.

9. (Rejected) Process according to claim 1, wherein excipients are added to the formulation after the filtration step, and wherein the conductivity of the HA formulation is measured in real time until the amount of excipients reaches a required value.

APPENDIX

CLAIM SUPPORT AND DRAWING ANALYSIS SECTION
(37 C.F.R. §41.37(e)(11))

1. (Rejected) A process for preparing a sterile ready-to-use aqueous pharmaceutical formulation comprising a high molecular weight hyaluronic acid salt (HA) at a specified concentration, comprising the steps of :

- providing an aqueous formulation comprising high molecular weight HA at a concentration of less than the specified concentration;

- passing said aqueous formulation through a filter having a pore size less than 0.45 μm; and greater than 0.1 μm **{p 3 [0050], lines 4-8}**;

- concentrating said aqueous formulation by applying a vacuum and boiling off water until said specified concentration is reached; and

- after the concentration step, filling the pharmaceutical formulation directly into sterile recipients ready for pharmaceutical use, or into sterile tanks and subsequently directly into sterile recipients ready for pharmaceutical use **{p 2 [0030], lines 6-10; p 4 [0058], lines 1-7; original claim 2}**.

2. (Cancelled)

3. (Cancelled)

4. (Rejected) Process according to claim 1, wherein the vacuum is at a pressure in the range of 30 to 60 millibars.

5. (Rejected) Process according to claim 1, wherein the average molecular weight of HA is in the range of 800'000 to 5'000'000 Daltons.

6. (Rejected) Process according to claim 1, wherein the filter has a pore size in the range of 0.22 μm to 0.1 μm **{p 3 [0050], lines 4-8; original claim 6}**.

7. (Rejected) Process according to claim 1, wherein, during the concentration step, the concentration of HA is measured in real time and the vacuum boiling process is stopped automatically when the specified concentration is measured.

8. (Rejected) Process according to claim 1, wherein the HA concentration is measured with a spectrophotometer sensing wave radiation absorption in the formulation.

9. (Rejected) Process according to claim 1, wherein excipients are added to the formulation after the filtration step, and wherein the conductivity of the HA formulation is measured in real time until the amount of excipients reaches a required value.

APPENDIX

MEANS OR STEP PLUS FUNCTION ANALYSIS SECTION
(37 C.F.R. §41.37(e)(11))

There are none.

APPENDIX

EVIDENCE SECTION
(37 C.F.R. §41.37(e)(11))

There is none.

APPENDIX

RELATED CASES SECTION
(37 C.F.R. §41.37(e)(11))

There are none.